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REVIEW

Commercial Diagnostics and Emerging Precision Medicine Technologies in Psoriasis and Atopic Dermatitis

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Abstract: While psoriasis and atopic dermatitis (AD) are two common dermatological conditions, their diagnosis and therapeutic decision-making pathways are often complex. As a result, there has been increased focus on the development of precision medicine approaches for psoriasis and AD. Two companies at the forefront of dermatology precision medicine research are Mindera Health and Castle Biosciences. Here, we review the technologies developed by these two companies using a dermal diagnostic patch and superficial skin scrapings, respectively, their research published to date, and their future research goals. Research from both companies shows promise in predicting the response of inflammatory skin disease to biologics using minimally invasive techniques. However, challenges to adoption include insurance coverage and patient trust in the technologies. While there are several differences between Mindera Health and Castle Biosciences, they have a shared goal of utilizing minimally invasive technologies to sample skin and predict response to biologic treatments using a panel of optimized biomarkers.

Keywords: machine learning, genetics, technology, diagnosis

Introduction

Psoriasis and atopic dermatitis (AD) are both common, immune-mediated, inflammatory skin diseases with significant physical and mental impacts. Psoriasis affects 2–4% of the Western population, with incidence continuing to increase.[1,2] Plaque psoriasis is the most common subtype, which is characterized by well-demarcated erythematous plaques with overlying silver-white scale commonly on the extensor surfaces, scalp, lumbosacral area, and gluteal cleft.[3] Psoriasis affects more than just skin, and is associated with co-morbidities such as cardiovascular disease, metabolic syndrome, and psoriatic arthritis.[1] Atopic dermatitis (AD) is characterized by pruritus and recurrent eczematous lesions.[4] It is the leading cause of skin disease worldwide, affecting up to 20% of children and 10% of adults.[5] AD has also been associated with co-morbidities such as the "atopic triad" of AD, asthma, and allergic rhinitis.[6]

Despite the development of many new topical and systemic therapies for psoriasis and AD, several clinical challenges remain. While most cases of psoriasis and AD can be readily diagnosed by physical examination and patient history, some cases have features of both psoriasis and AD leading to diagnostic confusion. This can lead to the use of incorrect treatments and worsening of disease and morbidity for the patient. While skin biopsies for histopathological examination can sometimes be helpful, biopsies are invasive, and providers more often opt to treat empirically rather than confirm with a biopsy, according to a recent retrospective analysis.[7] Non-invasive tests that reliably distinguish between psoriasis and AD could prevent misdiagnosis and trial-and-error therapies.

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Furthermore, selection of the best treatment for a particular patient with psoriasis or AD is another question dermatologists face. Patients may fail their initial treatment and then try several therapies before finding one that works for them. This process of trial and error can lead to many months of inadequately controlled disease and patient frustration. A 2022 survey of 195 participants with chronic inflammatory skin diseases (psoriasis n = 64; AD n = 101) revealed that poor disease control impacts patients' ability to perform daily activities and work productivity compared to moderately or well-controlled disease.[8] These potential psychosocial and personal economic impacts highlight the importance of selecting effective therapies for patients. In precision medicine, patients are classified into subpopulations that differ in response to various treatments.[9] Predictive biomarkers, such as genetics, genomics, or epigenetics, can guide this subclassification.

Mindera Health (Vista, CA) and Castle Biosciences, Inc. (Friendswood, TX) are companies that aim to develop non-invasive approaches for inflammatory skin disease diagnosis and therapeutic prognosis. In this review, we discuss the commercially available Mindera Health "Mind.Px™" patch test to guide psoriasis biologic selection. We also explore ongoing clinical studies by Castle Biosciences examining gene expression profiling for the diagnosis of psoriasis/AD, and for the prediction of treatment outcomes in psoriasis and AD.

Results

Mindera Health

Mindera Health is a company focusing on precision medicine. Their two primary technologies–SkinAtlas and Mind.Px™–focus on predictive skin models to help clinical decision-making.[10] The SkinAtlas is a database comprised of patient images, health data, and various skin samples. It applies artificial intelligence (AI) and machine learning across these data points to perform more comprehensive analytics related to therapy response.[10] Mind.Px™ is a United States (US)-patented dermal diagnostic patch composed of microneedles that sample ribonucleic acid (RNA) from the skin of patients with psoriasis.[11] Then, using next-generation sequencing (NGS) and machine learning algorithms, they analyze these samples for biomarkers to predict therapeutic response anti-TNFα, anti-IL-17, or anti-IL-23 psoriasis biologics.[10,12] Patients are categorized as responders or non-responders, and the obtained information is used to assist in treatment choice, minimizing diagnostic trial-and-error.[12,13]

Initially, Mindera Health assessed the demand for personalized diagnostic technology to establish a market position in the medical field. Wu et al demonstrated the financial implications of precision medicine in treating psoriasis.[14] Using a budget impact model from a US payer perspective (excluding Medicare and Medicaid), they demonstrated that Mind.Px™ would save patients with moderate-to-severe psoriasis an average of $8492 annually across six formulary options. Strober et al pursued a more clinical assessment by surveying 43 community dermatologists.[15] Their first survey demonstrated that the most significant factor impacting biologic therapy prescriptions was medication response. They also noted that first-line biologic therapies had a high failure rate, often necessitating a switch to a different therapy. The next survey followed an educational webinar describing Mind.Px™ as a diagnostic tool and all 43 providers stated that if incorporated into the prior authorization process, they would use Mind.Px™. Together, these two studies demonstrate the possible economic and clinical impact of Mind.Px™ on psoriasis treatment.[14,15]

Three clinical studies evaluated the Mind.Px™ dermal patch: STAMP-1, STAMP-2, and MATCH.[12,13] The STAMP studies were a series of observational studies that assessed the efficacy of Mindera's machine learning-based classifier algorithm.[12] The studies involved 242 patients with moderate-to-severe psoriasis who were tested before and after a 12-week treatment period with a TNF-α, IL-17, or IL-23 inhibitor.[12] Three predictive classifiers–groups of genes associated with treatment response–for each biologic therapeutic class were first determined from publicly available patient databases or early STAMP patients.[12] The genes were prospectively validated as response classifiers in the STAMP study based on achieving a 75% improvement in the psoriasis area and severity index (PASI) at week 12. In patients with a week zero PASI ≥ 8, the positive predictive value (PPV) in the three response classifiers was 85.7% for TNFi, 92.3% for IL-17i, and 93.1% IL-23i.[12] A list of the genes in each of the three response classifiers can be found in Supplemental Table 1.[11] Overall, 99.5% of patients were predicted to be responders, with only one predicted to be a non-responder to all three biologic classes.[12] Interestingly, there was a higher PPV in all three classifiers in patients with a week 0 PASI ≥ 10 (TNFi: 100.0%; IL-17i: 90.0%; IL-23i:

95.7%) and a lower PPV in patients with a PASI < 8 (ranging from 44.4% to 52.8%). The MATCH study validated the physician questionnaire published by Strober et al[13,15] In this study, 122 patients switching biologics or biologic naïve underwent biomarker analysis at week 0 with Mind.Px™.[13] Patients were split into the informed and uninformed groups. Providers were made aware of the results from the Mind.Px™ test in the informed group and not in the uniformed group. In the informed group, 84.4% of physician therapeutic decision-making corresponded to the results of Mind.Px™, while in the uninformed group, only 53.8% matched. The most common reason for informed physicians not choosing the Mind.Px™ outcome was due to payer formulary influences. Furthermore, informed patients achieved PASI75 sooner than uniformed patients ($p = 0.004$), demonstrating an important clinical benefit of Mind.Px™.

Castle Biosciences

Castle Biosciences is a diagnostics company that seeks to develop technologies that reveal information about each patient's unique biology and allow clinicians to use this information to make decisions that optimize health outcomes.[16] With already developed decision aids for melanoma and cutaneous squamous cell carcinoma, Castle is now moving into the inflammatory skin disease space. Castle's non-invasive approach to collecting skin samples involves superficial skin scrapings preserved in a proprietary buffer for analysis (Figure 1).

Currently, Castle is running a multi-site longitudinal clinical study to determine the utility of skin scrapings in inflammatory dermatoses, with the hypothesis that a multi-algorithmic gene expression profile (or profiles) can be identified to guide systemic therapy selection in patients with psoriasis, AD, and related conditions. The study is ongoing, but preliminary results are promising. Supporting the rationale for the study, scrapings of the superficial epidermis of lesional and non-lesional skin were collected from 20 psoriasis and 20 AD patients and immediately preserved in a proprietary buffer from two dermatology centers.[17] Twenty-eight genes were then analyzed using real-time polymerase chain reaction (RT-PCR) of lesional RNA. Five genes were increased in lesional AD versus non-lesional AD samples, whereas 7 genes were increased and 1 gene was decreased in psoriasis lesional versus non-lesional samples.[17] Additionally, AD lesional samples had increased expression of 7 genes compared to psoriasis lesional samples with 2 of these genes also exhibiting increased expression compared to the non-lesional samples. These results indicate that a non-invasive skin scraping provides adequate RNA to assess gene expression by quantitative RT-PCR to help distinguish between AD and psoriasis.[17]

Similar results from three dermatology centers were found after analysis of skin scrapings using a standardized procedure involving skin prep with alcohol, gently scraping the skin 10 times, and a human quality check before storage in the proprietary buffer.[18] Researchers found that when comparing AD lesional and non-lesional skin, 1633 RNA transcripts were differentially expressed. Additionally, 4468 transcripts were differentially expressed between psoriasis lesional and non-lesional skin. In addition to differentiating between lesional and non-lesional samples, AD and psoriasis could be distinguished as such by their respective gene expression profiles. The researchers suggest that clinical correlation with therapy outcomes based on these unique genetic profiles could be used to develop an algorithm to predict response to treatment.[18]

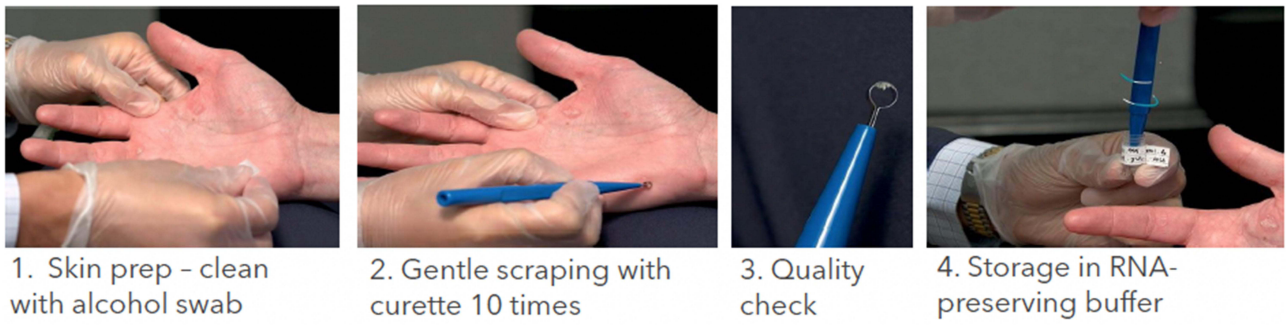

Figure 1 Skin scraping procedure used for collection of samples for Castle Biosciences. Image courtesy from Castle Biosciences, Inc.

One clinical diagnosis that can mimic psoriasis or AD is mycosis fungoides (MF), the most common variant of cutaneous T-cell lymphoma.[19,20] Early MF presents as erythematous patches/plaques and lasts for many years without harm. However, early diagnosis is crucial to avoiding inappropriate treatment, including some immunosuppressants used in other inflammatory skin diseases to prevent adverse outcomes.[19] Currently, MF requires pathological evaluation of lesional skin with sometimes multiple biopsies followed by additional molecular and immunohistochemical analysis for diagnosis.[19,20] Samples from 76 patients, where 24 were diagnosed with AD, 48 with psoriasis, and 4 with early stage (T1A) MF were analyzed using the Castle gene expression profile technology. Researchers observed significant gene expression differences, defined as log2 fold change of > absolute value 1, between the MF, AD, and psoriasis lesions.

With regard to therapeutic prediction, a subset of AD patients taking dupilumab and a subset of psoriasis patients taking risankizumab were followed over a course of 3 months to assess clinical response to dupilumab.[20] Researchers found that AD lesions from dupilumab "super-responders" defined as subjects exhibiting at least 90% improvement in the Eczema Area and Severity Index (EASI90) exhibited a distinct gene expression pattern compared to other AD patients on dupilumab.[20] Similar results were seen in patients who achieved at least 90% improvement in the Psoriasis Area and Severity Index (PASI90) with risankizumab. These results indicate that not only do superficial skin-scrapings have the potential to distinguish between psoriasis, AD, and even MF lesions but also predict an individual's response to systemic therapy.

A significant limitation of the above results is the small sample sizes. However, after Castle Biosciences completes their data collection, a more robust analysis can occur.

Discussion

With current treatment guidelines recommending a trial of biologic therapy for 12–16 weeks and the increasing number of biologics available, physicians and patients are left with many time-consuming and expensive choices.[21] According to joint American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) recommendations, further research is required to identify biomarkers that can predict individual patient responses to psoriasis biologic therapies.[21] Castle Biosciences and Mindera Health are attempting to fill this research gap by developing their respective technologies.

Mindera Health and Castle Biosciences differ in several ways, but they both strive to create minimally invasive technologies that gather skin samples to analyze genetic biomarkers.[10,17] Additionally, they leverage the large number of effective biologics to their advantage.[21] Mindera Health has focused on therapy response rather than diagnostic potential and has only published research on psoriasis.[12,13] They used public databases and a limited number of study patients with a PASI > 10 to identify response genes to biologics from three distinct classes.[12] As such, they had challenges demonstrating a significant positive predictive value (PPV) in patients with less severe disease, and whether their findings can be extrapolated to other biologics from the same class remains unknown.[12] Despite this, they have demonstrated the real-life clinical benefits of their technology in patient outcomes and continue to research treatment "super-responders" and "super-non-responders".[12,13] They have also published foundational findings on the economic need and physicians' willingness to use such a device, emphasizing the utility of their technology.[14,15] Of note, Mindera Health recently partnered with Liviniti, a pharmacy benefit manager, to provide self-funded employers with pass-through pricing of biologics to decrease medication costs.[22] In comparison, Castle Biosciences is using its research to identify specific genes related to atopic dermatitis, psoriasis, and mycosis fungoides, highlighting the diagnostic promise of their skin scrapings.[18,20] They have more recently investigated therapy response genetics, identifying gene expression differences in dupilumab and risankizumab "super-responders."[20] Whether their technology is predictive over a wide range of PASI scores is unknown. They have yet to achieve a US patent for their technology or publish a paper with the results of their studies, which are still ongoing.

Despite Mindera's recent partnership with Liviniti, a shared challenge for both companies will be insurance coverage and place within the diagnostic and treatment pathway. For these two technologies to have the greatest success, insurance companies must be willing to provide coverage and use their results as part of the prior authorization pathway. Furthermore, patient preference is of great importance, and despite receiving such results, patients may still choose to

pursue specific treatment pathways that align with their lifestyle and comorbidities. The true impact on healthcare will depend on the ease of implementation, accessibility, and patient trust of these technologies.

Conclusion

A review of Mindera Health and Castle Biosciences demonstrates that both companies are attempting to become leaders in precision medicine technologies, but with different approaches. Mindera Health has focused its efforts on developing the Mind.Px™ dermal patch and using this patch to identify psoriasis treatment response genes, while Castle Biosciences has focused on using their skin scraping technology to identify diagnostic and treatment response genes in both psoriasis and AD. The results of Castle Bioscience's ongoing multi-site study remain to be seen, but their preliminary data are promising. Further research is needed to determine if predictors of response can be generalized for a particular biologic class (ie if a patient responds to one IL-23 inhibitor, they will respond to another). As these two companies continue to evolve and advance, they will face similar challenges, such as practical application in a dermatology clinic. However, both are striving to improve the way skin diseases are diagnosed and treated. If successful, these companies could help reduce the significant morbidity of uncontrolled inflammatory skin disease.

Abbreviations

AD, Atopic dermatitis; US, United States; MF, Mycosis fungoides; RNA, ribonucleic acid; PPV, positive predictive value; NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction; PASI, psoriasis area and severity index; AAD, American Academy of Dermatology; NPF, National Psoriasis Foundation.

Disclosure

T.B. is currently a principal investigator for studies being sponsored by Amgen, Castle, CorEvitas, Pfizer, and Regeneron. She has additional research funding from Novartis and Regeneron. She has served as an advisor for AbbVie, Arcutis, Boehringer-Ingelheim, Bristol Myers Squibb, Dermavant, Janssen, Leo, Lilly, Pfizer, Novartis, Sanofi, Sun, and UCB. W. L. has received research grant funding from Amgen, Janssen, Leo, Novartis, Pfizer, Regeneron, and TRex Bio. A.S.F is an advisor for Castle Biosciences Inc. The authors report no other conflicts of interest in this work.

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